REMARKS

Claims 1-9, 11-38, 40, 50, 55, 60, and 80-87 are pending, with claim 55 having been withdrawn from consideration. Claims 1, 11-14, 23, 38, 50, and 60 have been amended herein. No new matter has been added with the Amendments, being fully supported by the specification and claims as originally filed. Upon entry of this communication, claims 1-9, 11-38, 40, 50, 60, and 80-87 will be under consideration.

Rejections under 35 U.S.C. § 112, Second Paragraph

Claims 1-9, 11-38, 40, 50, 60, and 80-87 stand rejected under 35 U.S.C. § 112, first paragraph as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Applicants respectfully traverse.

Claim 1, and dependent claims 2-9, 11-22, 80, 83, and 85-87, are rejected as allegedly lacking antecedent basis for the limitation "the target protein" in claim 1. Applicants have amended claim 1 by deleting the subject phrase and inserting "the reporter moiety" therefor. Applicants respectfully submit that antecedent basis for the limitations of amended claim 1 exists, and request withdrawal of the rejection.

Claim 23, and dependent claims 24-37 and 81, are rejected as allegedly being indefinite because the phrase "a α-NH-ubiquitin protein endoproteases" is unclear as to whether the claim is intended to encompass one or more α-NH-ubiquitin protein endoproteases. Applicants have amended claim 23 by deleting "a" from the subject phrase. Applicants respectfully submit that amended claim 23 is clear and definite, and request withdrawal of the rejection.

Claim 23, and dependent claims 24-37 and 81, are further rejected as allegedly lacking antecedent basis for the limitation "said protein of interest" in claim 23. Applicants have amended claim 23 by deleting the subject phrase and inserting "said target protein" therefor. Applicants respectfully submit that antecedent basis for the limitations of amended claim 23 exists, and request withdrawal of the rejection.

Claim 38, and dependent claims 40, 82, and 84, are rejected as allegedly being indefinite because the phrase "a α-NH-ubiquitin protein endoproteases" is unclear as to

whether the claim is intended to encompass one or more α-NH-ubiquitin protein endoproteases. Applicants have amended claim 38 by deleting "a" from the subject phrase. Applicants respectfully submit that amended claim 38 is clear and definite, and request withdrawal of the rejection.

Claim 50 is rejected as allegedly lacking antecedent basis for the limitation "said reporter moiety." Applicants have amended claim 50 by deleting the subject phrase and inserting "the target protein" therefor. Applicants respectfully submit that antecedent basis for the limitations of amended claim 50 exists, and request withdrawal of the rejection.

Claim 50 is further rejected as allegedly being indefinite because the phrase "a α-NH-ubiquitin protein endoproteases" is unclear as to whether the claim is intended to encompass one or more α-NH-ubiquitin protein endoproteases. Applicants have amended claim 50 by deleting "a" from the subject phrase. Applicants respectfully submit that amended claim 50 is clear and definite, and request withdrawal of the rejection.

Claim 60 is rejected as allegedly lacking antecedent basis for the limitations "said multimerized destabilization domain," "said reporter moiety," and "said linker." Applicants have amended claim 60 by deleting the subject phrases and inserting "said linear multimerized destabilization domain," "said target protein," and "said linker moiety" respectively therefor. Applicants respectfully submit that antecedent basis for the limitations of amended claim 60 exists, and request withdrawal of the rejection.

Claim 60 is further rejected as allegedly being indefinite because the phrase "a α-NH-ubiquitin protein endoproteases" is unclear as to whether the claim is intended to encompass one or more α-NH-ubiquitin protein endoproteases. Applicants have amended claim 60 by deleting "a" from the subject phrase. Applicants respectfully submit that amended claim 60 is clear and definite, and request withdrawal of the rejection.

In view of the above-listed amendments, Applicants respectfully submit that amended claims 1, 23, 38, 50, and 60 meet all requirements under 35 U.S.C. § 112, Second Paragraph, and reconsideration and withdrawal of the rejection are respectfully requested.

Rejections under 35 U.S.C. § 112, First Paragraph

Claims 1-9, 11-38, 40 and 80-87 stand rejected under 35 U.S.C. § 112, first paragraph as allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Applicants respectfully traverse the rejection.

Claims 1-9, 11-38, 40 and 80-87 are rejected as allegedly encompassing molecules, including ubiquitin homologs, for which there is insufficient written description provided in the specification. More specifically, the Examiner alleges that the specification at pages 13-14 defines the term "homolog" without satisfying the Written Description Guidelines, as disclosed on page 6 of the Office Action, for "ubiquitin homolog."

Applicants assert that the definition of "homolog" at pages 13-14 of the specification is meant to encompass a broad, general definition of the term. However, Applicants respectfully draw the Examiner's attention to page 24, lines 8-13, wherein destabilization domains and homologs thereof are disclosed. Specifically, "preferred as a destabilization domain is ubiquitin and homologs thereof, particularly mutants or homologs comprising mutations that prevent, or significantly reduce, the cleavage of ubiquitin multimers by α-NH-ubiquitin protein endoproteases." (Specification, page, 24, lines 8-11). The specification further defines the function of the destabilization domains (including homologs thereof) as "causing the target protein to be recognized by one or more elements of the cellular protein degradation apparatus." (Specification, page 24, lines 11-13). Thus, one of skill in the art would understand that the ubiquitin homologs of the invention would have the desired function of retaining ubiquitin function. Applicants submit that the definition of "homolog" at pages 13-14 of the specification combined with the disclosure at page 24 of the specification regarding destabilization domains satisfies the Written Description Guidelines. Consequently, Applicants respectfully request withdrawal of the rejection.

Claims 1-9, 11-22, 80, 83, and 85-87 are rejected as allegedly encompassing molecules, including reporter gene homologs (see claims 11-14), for which there is insufficient written

description provided in the specification. More specifically, the Examiner alleges that the specification at pages 13-14 defines the term "homolog" without satisfying the Written Description Guidelines, as disclosed on page 6 of the Office Action, for "reporter gene homologs." Applicants have amended claims 11-14 as suggested by the Examiner. Consequently, Applicants respectfully request withdrawal of the rejection.

Claims 1-9, 11-38, 40 and 80-87 also stand rejected under 35 U.S.C. § 112, first paragraph as allegedly containing subject matter which was not described in the specification in such a way as to enable one killed in the art to which it pertains to make or use the invention. Specifically, the Examiner alleges that without a clear description of the homologs encompassed by the claims, one of skill in the art would not know how to make or use the claimed invention without performing additional experimentation. Applicants respectfully traverse.

The arguments presented above regarding the ubiquitin homologs apply equally here. In *In re Brana*, the Federal Circuit held that "[u]sefulness in patent law, and in particular in the context of pharmaceutical inventions, necessarily includes the expectation of further research and development. The stage at which an invention in this field becomes useful is well before it is ready to be administered to humans" (*In re Brana*, 51 F.3d 1560, 1568 (Fed.Cir.1995). Whether undue experimentation is required is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations. As stated by the Examiner at page 8 of the Office Action, factors to be considered include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. *In re Wands*, 858 F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988). Some trial and error is permissible. *W.L. Gore & Assoc. v. Garlock, Inc.*, 721 F.2d 1540, 220 USPQ 303 (Fed. Cir. 1983). Applicants submit that definition of "homolog" provided at pages 13-14 of the specification and the discussion regarding destabilization domains and the functionality thereof is sufficient to satisfy the Written Description and Enablement

requirements of 35 U.S.C. § 112, first paragraph. It is therefore submitted that one of skill in the art would understand how to make and use the methods of the invention with ubiquitin homologs as destabilization domains. Accordingly, reconsideration and withdrawal of the rejection under 35 U.S.C. § 112, first paragraph, are respectfully requested.

Claims 1-9, 11-38, 40 and 80-87 further stand rejected under 35 U.S.C. § 112, first paragraph as allegedly lacking enablement for the full scope currently encompassed by claim 1. Specifically, the Examiner alleges that the claim encompasses "modification" of the linker moiety by the protease activity wherein modification could be an activity other than protease activity. Further, the Examiner alleges that use of the terms "modulate" and "modulating" in reference to the coupling of the destabilization domain to said reporter moiety, and to the stability of said reporter moiety encompasses both the ability to increase and the ability to decrease the coupling and stabilization. Applicants have amended claim 1 as suggested by the Examiner to clarify the function of the protease activity and its effect upon the coupling of the destabilization domain to said reporter moiety. Consequently, Applicants respectfully request withdrawal of the rejection.

Claims 23-37 and 81 stand further stand rejected under 35 U.S.C. § 112, first paragraph as allegedly lacking enablement for the full scope currently encompassed by claim 23. Specifically, the Examiner alleges that because the claim is drawn to a method of "regulating" the concentration of one or more target proteins in a cell, it encompasses both increasing and decreasing the concentrations of the target proteins. Further, the Examiner alleges that use of the terms "modulate" and "modulating" in reference to the coupling of the destabilization domain to said reporter moiety, and to the stability of said reporter moiety encompasses both the ability to increase and the ability to decrease the coupling and stabilization. Applicants have amended claim 23, as suggested by the Examiner, to encompass a method of increasing the concentration of target proteins, and to clarify the function of the protease activity and its effect upon the coupling of the destabilization domain to said reporter moiety. Consequently, Applicants respectfully request withdrawal of the rejection.

Accordingly, Applicant respectfully requests withdrawal of the rejections under 35 U.S.C. § 112, first paragraph.

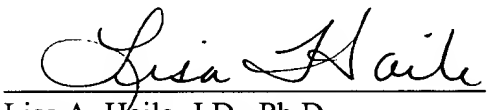
CONCLUSION

In view of the amendments and the above remarks, it is submitted that the claims are in condition for allowance and a notice to that effect is respectfully requested. The Examiner is invited to contact Applicants' undersigned representative if there are any questions relating to this application.

Please charge any additional fees, or make any credits, to Deposit Account No. 50-1355.

Respectfully submitted,

Date: May19, 2004



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